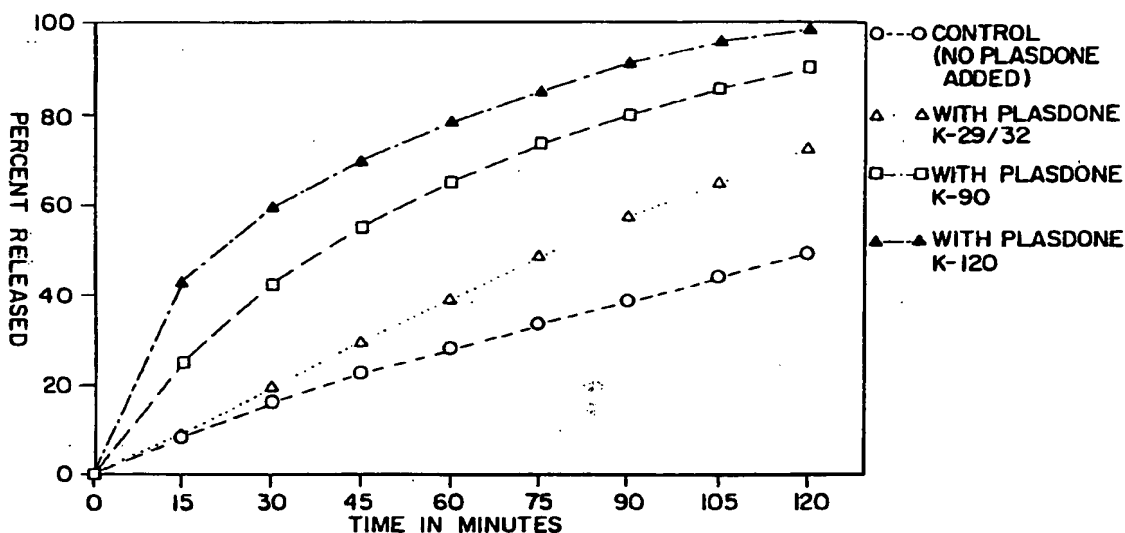




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(71) Applicant: ISP INVESTMENTS INC. [US/US]; 818 Washington Street, Wilmington, DE 19801 (US).			
(72) Inventors: CHAUDHURI, Ratan, K. ; 74 Reservoir Avenue, Butler, NJ 07475 (US). JAISWAL, Dinesh, K. ; 1581 Route 23, Apt. 4, Butler, NJ 07475 (US). HALDAR, Rama, K. ; 8 Sweetwood Drive, Randolph, NJ 07869 (US). LOGIN, Robert, B. ; 137 Page Drive, Oakland, NJ 07436 (US). TAZI, Mohammed ; 3383 Bridle Run Trail, N.W., Marietta, GA 30064 (US). CHUANG, Jui-Chang ; 110 Overlook Avenue, Wayne, NJ 07470 (US).			

(54) Title: PHARMACEUTICAL TABLET WITH PVP HAVING AN ENHANCED DRUG DISSOLUTION RATE



## (57) Abstract

A pharmaceutical tablet is provided herein having an effective dissolution rate. The tablet contains a pharmaceutically-active ingredient and a substantially linear, i.e. non-crosslinked K-30 to K-120 PVP, preferably above 116, as a binding agent. The PVP used herein preferably is made by a polymerization process in which the vinyl pyrrolidone monomer is polymerized in the presence of an initiator which produces a linear PVP polymerization, and a residual initiator level of less than 500 ppm.

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PHARMACEUTICAL TABLET WITH PVP  
HAVING AN ENHANCED DRUG DISSOLUTION RATE

This invention relates to a pharmaceutical tablet containing polyvinylpyrrolidone (PVP) as a binder for a pharmaceutically-active ingredient therein, and more particularly, to such tablets which dissolve readily in water to release their active material even after the product has experienced a considerable period of shelf-time.

PVP is used widely as a binding agent for pharmaceutical tablets. However, it is essential that the PVP binder itself not interfere with the normal dissolution rate of the tablet in water. Suitable PVP polymers presently used as a binder agent in pharmaceutical tablets are prepared by free radical polymerization in the presence of a free radical initiator, as described in Polymer Journal 17, No. 1, p 143-152 (1985). These free radical polymerization initiators are used in amounts of about 0.05 to 10% by weight of the monomer, and, preferably about 0.1 to 5% by weight of an initiator is required. Hydrogen peroxide, di-t-butyl peroxide, dicumyl peroxide, t-butylperoxy pivalate (TBPP) and t-butylperoxy benzoate (TBPB) are widely used free radical polymerization initiators for the preparation of PVP polymers. TBPP, for example, undergoes thermal homolysis to produce t-butoxy and t-butyl free radicals.

The methyl and t-butoxy free radicals, respectively, have high bond dissociation energies (BDE) of 104 and 105 kcal/mole, respectively. Therefore, these radicals can readily abstract a labile hydrogen atom from the PVP polymer to transfer the site of initiation and hence convert an otherwise linear polymer into a branched polymer. If this process is carried too far, the PVP

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polymer produced will have poor water solubility and/or become gels. In addition, the half-life of such TBPP initiator, i.e. the time at a given temperature to effect a loss of one-half of the perester's active oxygen content, is a lengthy 24.6 hours at 50°C. Accordingly, TBPP requires a high reaction temperature, e.g. 60°-80°C., to carry out the polymerization within a reasonable period of time. Accordingly, the choice of initiator is critical to preclude the formation of branched rather than linear PVP polymers both during polymerization and afterwards during ageing of pharmaceutical tablets containing such PVP as a binding agent.

A pharmaceutical tablet is provided herein containing a pharmaceutically-active ingredient and a K-30 to K-120, preferably above 116, PVP as a binding agent, suitably about 0.5-10% by weight, preferably about 5%. Preferably, the PVP is made by a free radical initiated polymerization process in which vinylpyrrolidone monomer is polymerized in the presence of a low energy peroxy radical initiators, such as t-amylperoxy pivalate (TAPP), an azo initiator, or a redox initiator, and at the lowest possible reaction temperatures. These named initiator materials are effective polymerization initiators for PVP polymerization, but, because of their structure, i.e. they are relatively poor hydrogen abstractors in the backbone of the PVP polymer and/or the low polymerization temperature.

Azo initiators are preferred because they generate free radicals that are of low energy. A similar effect is obtained using a low temperature free radical initiator that has an acceptable half-life at lower temperatures because the rate expression for transfer to polymer is dependent on temperature.

Such polymerization processes of the invention are carried out at a lower temperature than similar polymerizations using conventional free radical initiators,

which themselves are active hydrogen abstractors. Because of the structure of the initiator, or because lower temperatures can be used, linear PVP polymers of high molecular weight which exhibit more rapid water solubility in use in pharmaceutical tablets are provided herein. Furthermore, the low transfer to polymer property of these initiators enable the residual initiator to be decomposed at elevated temperatures without causing crosslinking. For example, a PVP K-90 polymer mixture prepared in water can be post-heated at 60-80°C. to reduce the residual initiator level to less than 500 ppm.

Preferably the PVP obtained has a K-value in excess of 116, e.g. 119-140, and a viscosity average molecular weight\* of at least one million, a weight average molecular weight\*\* of at least two million, and a relative viscosity\*\*\* of at least 1.2, most preferably about 1.2-1.5. Preferably, also, the tablet contains a suitable

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\* determined using viscosity measurements method according to Scholtan, W.; Makromol. Chem., 7, 209 (1951).

\*\* determined by gel permeation chromatography using formula :  $\log Mw = 2.82 \cdot \log K \text{ value} + 0.594$

\*\*\* A single solution of the PVP sample is prepared in water at 1% w/v. The relative viscosity,  $\eta_{rel}$  is computed by dividing the flow time in seconds of the aforementioned solution (as determined in an Ostwald-Fenske capillary viscometer) by the flow time of water. The K-value is then obtained from Fikentsher's equation.

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filler and/or lubricant. In the most preferred form of the invention, the pharmaceutical tablet consists essentially of, by weight, about 10-98% of a poorly water-soluble drug, about 2-10% of PVP K-116-140, about 0.5-2% of a lubricant, 0-3% disintegrant and about 0-85% of a filler, and is prepared either by direct compression or by using wet granulation.

The pharmaceutical tablets provided herein are particularly characterized by a rapid dissolution rate even after a prolonged shelf-life; accordingly, the PVP polymer prepared and used herein performs its binding function without an accompanying adverse side effect of a reduced dissolution rate for the active material in the tablet.

In accordance with one embodiment of the invention, a free radical polymerization process for polymerizing vinylpyrrolidone to form PVP is provided herein. Preferably the free radical polymerization initiator is, (1) a peroxy ester which radicals are weak hydrogen abstractors, e.g. t-amylperoxy pivalate (TAPP); (2) an azo initiator, or (3) a redox catalyst. These initiators and catalysts provide low energy pathways during polymerization of VP monomer. The order of energy of polymerization, and hence the degree of crosslinking of PVP, is:

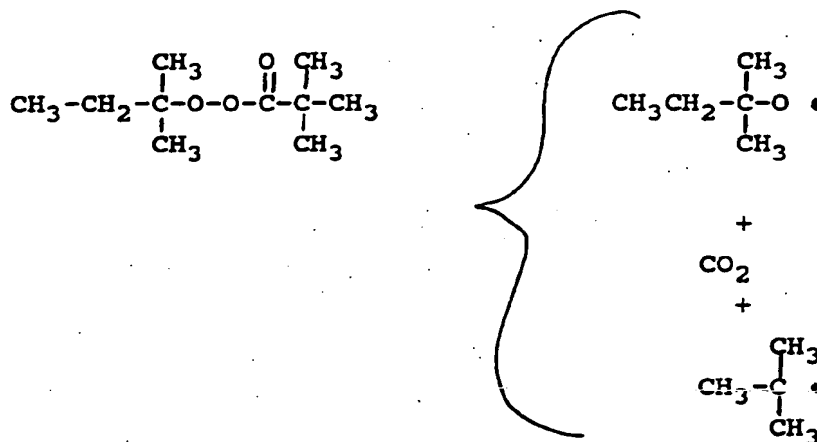
Redox	<	Azo	<	Peroxide;
Catalyst		Initiator		Initiator

and for peroxides

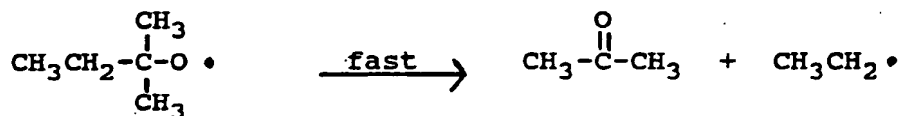
TAPP	<	TAPP	<	peroxy benzoates.
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TAPP, for example, undergoes thermal homolysis as follows:

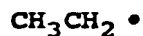
Thermal Homolysis of TAPP



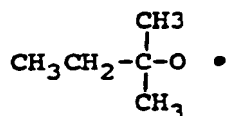
followed by  $\beta$ -scission of the t-amylloxy radical:



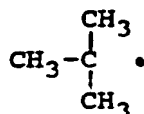
Accordingly the active free radical species of TAPP are:



ethyl radical



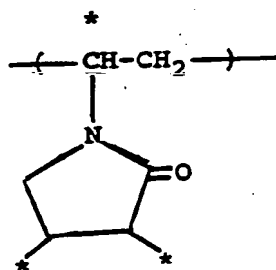
t-amylloxy radical



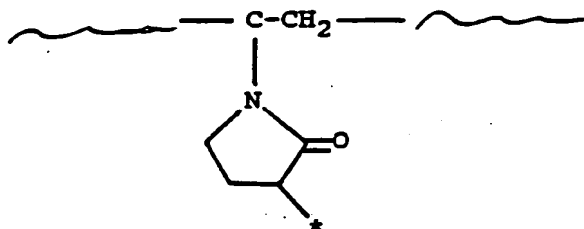
t-butyl radical

Th ethyl and t-amylloxy free radicals thus produced have a BDE of only 98 kcal/mole; therefore TAPP is a relatively weak hydrogen abstract r. Thus, substantially linear PVP polymers of high molecular weight and excellent water solubility are provided using the TAPP initiator of the invention.

More particularly, as shown below, polyvinylpyrrolidone formed by free radical polymerization of vinylpyrrolidone has several active hydrogen sites, indicated by the asterisks, for hydrogen abstraction by the active free radical species of TBPP.



which could produce the branched and crosslinked PVP polymers shown below:



TAPP, and other low energy or poor transfer to polymer initiators, on the other hand, have only weak hydrogen abstractors or are effective for polymerization at low temperatures, and produce substantially linear PVP polymers which exhibit excellent water dissolution, even after ageing.

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Furthermore, it is known that lower molecular weight polymers are produced when high polymerization temperatures or long reaction periods are required. TAPP, and azo and redox catalysts, can effect PVP polymerizations at lower temperatures, than these more active higher temperature initiators; therefore, it is possible to produce herein high molecular weight, linear PVP polymers using these defined initiators. TAPP, for example, can afford initiation and low residual peroxide residue after polymerization; furthermore it is a low energy producing radical generator with reduced capacity to extract a proton from the PVP polymer. This fact enhances the stability of the PVP polymer. Even if it contains some initiator residue, it will pass the tests used to determine tablet stability, e.g. accelerated ageing-dissolution testing. However, further heating of the formed polymer solution before drying to powder guarantees the reduction of the amount of active initiator to very low levels (< 500 ppm). This post polymerization step occurs without branching or crosslinking because of the poor ability of the initiator to abstract protons from the PVP chain.

The t-amylperoxy pivalate initiator, for example, can be employed in the polymerization of vinylpyrrolidone in an amount of about 0.01 to 10% by wt. of the monomers, preferably about 0.1 to 5%.

The PVP polymers thus-produced are characterized by substantially water soluble (more linear, less branched), of stable molecular weight than PVP polymers made with more aggressive free radical initiators.

The t-amylperoxy pivalate may be obtained from the Pennwalt Corp. under their trade name of Lupersol 554M75, which is sold as a 75% by weight active solution in odorless mineral spirits.

Suitable azo-type initiators for use herein include 2,2'-azobis(isobutyronitrile), often referred to as AIBN, which is sold by Dupont under the trad name Vazo 64; 2,2'-azobis(2-methylbutanenitrile), which is Vazo 67; 2,2'-azobis(2,4-dimethylpentanenitrile), often referred to as ABVN, which is Vazo 52; 1,1'-azobis(cyclohexanecarbonitrile), Vazo 88; 2,2'-azobis(2-methylpropanimidamide) dihydrochloride; 2,2'-azobis(2-acetoxypropane; 2-tert-butylazo) isobutyronitrile; 2(tert-butylazo)-2-methylbutanenitrile; and 1-(tert-butylazo) cyclohexane-carbonitrile, sold by Pennwalt as Luazo 79, Luazo 82 and Luazo 96, respectively.

These azo-type initiators generate highly selective tertiary alkyl radicals which have a reduced propensity to attack the backbone of the polymer. This effect reduces chain branching and crosslinking and should free radicals be generated in subsequent polymer storage (even after the post polymerization heating step designed to assure very low levels of residual initiator) prevents the possibility of further reactions such as crosslinking.

A lower energy is required to generate radicals by a redox mechanism; hence the reaction is carried out at lower temperatures which does not favor transfer to polymer. If a slight excess of reducing agent is employed, no residual peroxide is available at the end.

Addition of small quantities of reducing agents to peroxides greatly accelerates radical generation. Such Redox initiators, i.e., systems based on mixtures of oxidizing and reducing agents, initiate through the occurrence of one-electron transfer steps that form free-radical intermediates. Free-radical polymerization is used in redox mechanisms, as for example, in the system ferrous ion plus hydrogen peroxide (Fenton's reagent), since it provides an intervention of free radicals and allows their rate of formation to be measured. Many redox initiators are known and numerous "recipes" are current in polymerization technology.

Red x initiators for use here in are classified according to their solubilities (in water or organic liquids) or their mode of radical generation.

The powerfully oxidizing properties of mixtures of hydrogen peroxide and ferrous salts, discovered by Fenton in 1894, are attributed to the participation of OH and  $\text{HO}_2$  radicals.

Organic peroxides or persalts such as potassium persulfate enter into similar reactions, which are essentially one-electron transfers with concomitant cleavage of the -O-O- bond.

Other transition metal ions such as  $\text{Ti}^{3+}$  can enter into similar reactions.

With potassium persulfate as oxidizing agent, the analogous reactions occur. Other metal ions react with persulfates generating free radicals. Reducing agents such as those containing sulfite salts convert ferric to ferrous ion and hence propagate the decomposition of the persulfate salts or organic peroxides to free radicals. The advantage is that this method of polymer initiation can occur at much lower temperatures as compared to homolytic peroxide cleavage.

For example, hydroperoxides are well-known components of redox systems and their reduction by ferrous salts has been investigated in detail. The primary step is the one-electron transfer and bond cleavage process. The product is an alkoxy rather than a hydroxyl radical. Among the hydroperoxides are cumene, p-menthane, and p-isopropylcumene. It is common practice to add a second reducing agent such as glucose, fructose, dihydroxyacetone, or sodium formaldehyde sulfoxylate to reduce the ferric ion formed to ferrous and so keep up the rate of initiation.

Strongly reducing metal ions may enter into redox processes with compounds other than peroxide; for example,  $\text{Ti}^{3+}$  can reduce hydroxylamine in acid solution to  $\text{NH}_2$  radicals. Other metal ions ( $\text{Cr}^{2+}$ ,  $\text{V}^{2+}$ ,  $\text{Fe}^{2+}$ ) behave

similarly. These combinations are capable of initiating VP polymerization.

In the redox systems so far discussed, the metal ion is the reducing component; however, many strongly oxidizing metal ions participate in single-electron transfer reactions, with free radical generation.

Systems in which two relatively stable salts form a redox pair may be used in the polymerizations herein. Typical oxidizing agents are potassium persulfate, potassium ferricyanide, ceric sulfate, potassium permanganate, t-butyl hydroperoxide, cumene hydroperoxide, pinane hydroperoxide, and diisopropylbenzene hydroperoxide. Reducing agents include sodium hyposulfite, sodium metabisulfite, sodium sulfide, sodium thiosulfate, and hydrazine hydrate. No transition metal derivatives are included in these examples. Both oxidizing and reducing components form free radicals, which, in principle, may initiate polymerization, although the behavior in any given system depends on the radical and monomer reactivities.

Organic peroxides may react in nonaqueous solution by redox processes. It has long been known that benzoyl peroxide can enter into relatively rapid reactions with primary, secondary, and tertiary amines.

The most familiar systems include diacyl peroxides and tertiary amines, of which benzoyl peroxide and dimethylaniline are typical. The reactants form a complex which cleaves into radicals.

In each of the above cases a reducing agent must be present to regenerate the ferrous ion. Examples would be sodium hyposulfite, sodium metabisulfite, sodium sulfide and sodium thiosulfate. Numerous recipes are available and are known to those skilled in the art.

Redox systems capable of free radical initiation can also be generated by the reaction of dibenzoyl peroxides and dimethylaniline, and other dialkyl peroxides

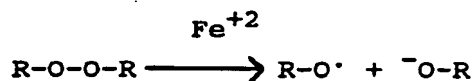
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and organic reducing agents such as those containing sulfinic acids, alpha-ketols, formic acid, thiols and hydrazines.

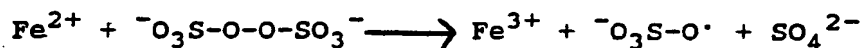
Obviously the literature of redox systems is quite extensive and has recently been reviewed by for example C.H. Bamford, page 123, V. 3 of "Comprehensive Polymer Science", (1989), G.C. Eastmond et al. editors.

Redox reactions have been applied to the polymerization of PVP. Apparently the low temperature polymerization of VP and potassium persulfate reported by S.N. Trubitsyna et al. (Izv. Vuzov SSSR, Khimiya i khim. Tekhnolgiya, Vol. 22, 720 (1979) is such an example.

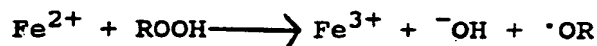
To achieve linearity, a source of radicals at the lowest possible temperature that efficiently promotes polymerization is theoretically the best approach to linear polymer synthesis. Hence water soluble redox reactions such as indicated below are possible.



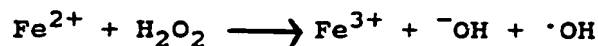
or



or



or



(Fenton's Reagent)

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IN THE DRAWINGS

FIGS. 1 and 2 are graphs representing dissolution rates, in percent drug released vs. time, from a pharmaceutical tablet containing PVP of differing K-values.

FIG. 3 is a graph representing compressibility, expressed in hardness (kp) vs. force (kg), for a pharmaceutical tablet containing PVP of differing K-values.

FIG. 4 is a graph representing friability, in percent vs. force (kg) for a pharmaceutical tablet containing PVP of differing K-values.

In accordance with another aspect of the invention, a pharmaceutical tablet is provided herein which has an enhanced drug dissolution rate and consists essentially of an active pharmaceutical ingredient and polyvinylpyrrolidone having a K-value in excess of 116, preferably 119-140. This PVP binder is present in an amount of about 0.5-10% by weight of the tablet. The product is further characterized by lower friability and superior compressibility, as compared to similar tablets using PVP of lower K-values. Preferably, the PVP of the present invention has a viscosity average molecular weight of at least one million, a weight average molecular weight of at least two million, and a relative viscosity of at least 1.2, most preferably about 1.2-1.5. Preferably, also, the tablet contains a suitable filler and/or lubricant. In the most preferred form of the invention, the pharmaceutical tablet consists essentially of, by weight, about 10-25% of poorly water-soluble drug, about 2-10% of PVP K-116-140, about 0.5-2% of a lubricant and about 65-85% of a filler, and is made by compression using wet granulation.

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Pharmaceutical tablets were prepared by direct compression (A) or using wet granulation followed by compression (B).

A. Tablets by Direct Compression

All ingredients, except magnesium stearate, were blended in a twin-shell blender for 12 minutes. Magnesium stearate then was added and blended for an additional three minutes. The mixture was then compressed on a Stokes B-2 rotary press to produce tablets of uniform weight (450 mg) and hardness of 8-10 KP.

B. Tablets by Wet Granulation

1. Granulating Solution - In each formulation the binder consisted of PVP K-140 or PVP K-120 or PVP K-90 (50 g.) or Plasdone K-29/32 (100 g.) dissolved in purified water (450 g. for PVP K-90 or Plasdone K-120 and 300 g. for PVP K-29/32). The mixing time was 30 minutes for all binder solutions.

2. Granulation - Acetaminophen (1500 g.) was transferred in a planetary mixer and 300 g. of the granulating solution was added slowly and mixed for 5 minutes at a speed number 1. To ensure even and complete granulation, the mixing blades and the bowl were scraped well with a spatula before allowing the granulation to mix for another 10 minutes at speed #2 (total mixing time - 15 minutes). The granulation end point was reached when the moistened powder mass had a "snowball" consistency and no dry powder was detected in the bowl. The sides of the mixer bowl could be easily cleaned by the movement of the formed granules.

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The wet milling step was accomplished by passing the granulation through a Newark #30 screen by hand. The milled batch was placed on paper-lined trays and introduced into an oven set at 40°C. for about 4 hours. The dried granules were passed through a 12-mesh screen using an oscillator (Erweka AR 400). Lubrication was performed by mixing magnesium stearate (0.5% of the weight of the milled batch to be tableted) for 3 minutes in a twin-shell v. blender.

3. Tableting - The tablets were compressed on a rotary tablet-press (Stokes B-2) to a targeted mass of 200 mg. The compressed force was also monitored during the tableting operation utilizing an oscilloscope.

A. TABLET BY DIRECT COMPRESSION

EXAMPLE 1

CONTROL (NO PVP)

<u>INGREDIENTS</u>	<u>PERCENT</u>
Sulfathiazole .....	22.2
Fast-Flo Lactose/Ditab (1:1) .....	76.8
Magnesium Stearate .....	<u>1.0</u>
	100.0

WITH PVP

Sulfathiazole .....	22.2
Fast-Flo Lactose/Ditab (1:1) .....	71.8
PVP K-29/32, PVP K-90, PVP K-120 or PVP K-140	5.0
Magnesium Stearate .....	<u>1.0</u>
	100.0

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EXAMPLE 2  
CONTROL (NO PVP)

<u>INGREDIENTS</u>	<u>PERCENT</u>
Hydrochlorothiazide .....	10.0
Fast-Flo Lactose/Ditab (1:1) .....	89.0
Magnesium Stearate .....	<u>1.0</u>
	100.0

WITH PVP

Hydrochlorothiazide .....	10.0
Fast-Flo Lactose/Ditab (1:1) .....	84.0
PVP K-29/32, PVP K-90, PVP K-120 or PVP K-140	5.0
Magnesium Stearate .....	<u>1.0</u>
	100.0

B. TABLET BY WET GRANULATION

EXAMPLE 3A

<u>WET GRANULATION</u>	<u>PERCENT</u>
Acetaminophen .....	83.0
PVP K-29/32 .....	4.2
Water .....	<u>12.8</u>
	100.0

EXAMPLE 3B

<u>WET GRANULATION</u>	<u>PERCENT</u>
Acetaminophen .....	83.3
PVP K-90, K-120 or K-140 .....	1.7
Water .....	<u>15.0</u>
	100.0

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<u>TABLET</u>	<u>PERCENT</u>
Acetaminophen Granule .....	99.5
Magnesium Stearate .....	<u>0.5</u>
	100.0

PERFORMANCE TESTS

1. Dissolution - This test was performed on tablets stored for more than 12 hours after compression, using USP dissolution apparatus 2 (Vanderkamp 6000) with a paddle rotational speed of 100 rpm. Aqueous 0.1 N-HCl was utilized as the dissolution medium (900 ml). The amount of sulfathiazole or hydrochlorothiazide released in the medium as a function of time was determined using a UV spectrometer which measured the peaks at 280 nm (sulfathiazole) and 272 nm (hydrochlorothiazide).

2. Hardness - The tablet hardness was determined 24 hours after compression using a Model HT-300 (Key International Inc.) hardness tester. 10 Tablets were tested for each batch and the mean value was calculated. Hardness is measured in kilopounds (KP) (1 KP = 9.8 Newtons).

3. Friability - 10 tablets were weighed and placed in a friabilation apparatus and rotated on a wheel for 4 minutes at 25 rpm. Then the tablets were placed on a screen to allow any powder to pass through. The 10 tablets were reweighed. The results are expressed as follows:

$$\text{Friability} = \frac{(\text{Initial weight}) - (\text{Final Weight}) \times 100}{\text{Initial Weight}}$$

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## RESULTS

### DISSOLUTION RATE PROFILE

FIGURE 1 AND 2. The T-60 (time to release 60% of the drug - See Table 1) for sulfathiazole and hydrochlorothiazide with Plasdone® K-120 is faster than with no Plasdone® (sulfathiazole - > 3.75 times; hydrochlorothiazide - 2.25 times); Plasdone® K-29/32 (sulfathiazole - > 1.14 times; hydrochlorothiazide - 1.55 times) and Plasdone® K-90 (sulfathiazole - > 2.18 times; hydrochlorothiazide - 1.73 times).

### COMPRESSION FORCE PROFILE

FIGURE 3. Plasdone® K-120 when compressed at 1500 kg. yielded tablets with 8-10 kp whereas Plasdone® K-29/32 and K-90 each required at least 2000 kg to yield tablets with the same hardness.

### FRIABILITY

FIGURE 4. Friability results for tablets containing Plasdone® K-120 at 1500 kg force were 0.9% (sulfathiazole), 0.5% (hydrochlorothiazide) whereas tablets made with Plasdone® K-29/32 and Plasdone® K-90 at the same compression force were 1.4% (sulfathiazole), 0.8% (hydrochlorothiazide) and 1.7% (sulfathiazole), 0.9% (hydrochlorothiazide) respectively.

TABLE 1

DISSOLUTION RATE OF TABLETS (T-60)

PHARMACEUTICALLY ACTIVE INGREDIENT			
TABLETS PREPARED BY USING	SULFATHIAZOLE (EX. 1)	HYDROCHLOROTHIAZIDE (EX. 2)	ACETAMINOPHEN (EXS. 3A and 3B)
No Plasdone® (Control)	> 120 min	90 min	-
Plasdone® K-29/32	105 min	58 min	222 min
Plasdone® K-90	55 min	52 min	128 min
Plasdone® K-120	32 min	40 min	95 min
Plasdone® K-140	19 min	30 min	81 min

TYPICAL PHARMACEUTICALLY - ACTIVE INGREDIENTS

Sulfathiazole	Sulfadiazine
Acetaminophen	Probenicid
Acetazolamide	Hydrochlorothiazide
Amoxicillin	Hydrocortisone
Aspirin	Hydroflumethiazide
Acetohexamide	Ibuprofen
Chloroambucil	Iodogninol
Chlorothiazide	Levodopa
Chloramphenicol	Mebendazole
Codeine	Mephobarbital
Diazepam	Meproamate
Diethylstibesterol	Methazolamide
Dipyramidole	Methotrexate
Frgocalciferol	Metronidazole
Frythromycin	Naproxen
Fluoxymesterone	Norfloxacin
Furazolidone	Oxymetholone
Glutethiamide	Oxyphenbutazone
Griseofulvin	Oxytetracycline
Polythiazide	Pindolol
Sulfamerazine	Sulfamethizole
Sulfamethoxazole	Trichlormethiazide

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Preparation of Polyvinylpyrrolidone  
(TAPP Initiator)

EXAMPLE 4

A 2-liter reactor provided with agitation, gas inlet, condenser, and thermocouple was charged with 270 g. (2.3 moles) of non-stabilized vinylpyrrolidone monomer, which was buffered with a solution of 0.27 g. of tetrasodium pyrophosphate in 1,080 g. of deionized water. The reactor was swept clean of oxygen by admitting nitrogen gas through the inlet tube. Then the reactor was heated to 55°C. and 0.25 g. of t-amylperoxy pivalate (TAPP) was added (< 0.1% by wt. of vinylpyrrolidone). The mixture was heated at 56°-59°C. for 5 hours, whereupon an additional 0.25 g. of TAPP was added and the reaction continued for 2 hours. At the end of the reaction period, the mixture was heated to 85°C. and held at this temperature until the residual peroxide level was less than 500 ppm. The product included 21% solids; the residual monomer content was 0.04%. The PVP polymer product in water thus-obtained was characterized by being substantially linear, a K-value of 90, low residual initiator level, and excellent water dissolution.

EXAMPLE 5 (t-BPP)

A 5-liter reactor equipped with a turbine agitator, N<sub>2</sub> gas subsurface sparge, condenser and thermocouple was charged with 3,326 g. of deionized water, 1.6 g. of NH<sub>4</sub>OH (38% NH<sub>3</sub>) and 2-5 ppm EDTA. Then was added 1,000 g. of unstabilized vinyl pyrrolidone, the mixture sparged with N<sub>2</sub> and heated to 55°C. t-Butylperoxy pivalate (0.23 g.) was added and the polymerization begun as evidenced by a modest exotherm.

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The temperature was maintained at 70-80°C. for 2 hours and residual VP measured. Small charges of t-BPP (0.05 grams) were added as required to bring the residual VP to below 0.1%. Thereafter the temperature was raised to 85°C. until residual peroxide was less than 500 ppm; the solids level was 17-18%. The aqueous solution then was dried and milled to provide the polymer in powder form.

EXAMPLE 6 (t-BPP)

A 12-liter four-necked flask equipped with mechanical stirrer, reflux condenser, thermometer, and glass stopper was purged with nitrogen for 15 minutes. 1150 g. of vinylpyrrolidone and 3850 g. of distilled water were then charged and a positive nitrogen pressure was maintained throughout the reaction. The reactants were heated to 55°C., in 20 minutes and 3 ml of t-butylperoxy pivalate was then added to the vinylpyrrolidone/water mixture through one of the necks of the flask. The temperature of the reactor was then maintained at 55°C. for 3 hours after which the system was heated to 80°C. in one-half hour and maintained at 80°C. for another 15 minutes. The reactor was then cooled to room temperature and the product discharged. The product had the following properties.

Density	0.8493 gm/ml
K value	91.1
APHA color	5/10
vinylpyrrolidone	0.054 wt %

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EXAMPLE 7

The procedure of Example 4 was followed using 2,2'-azobis(isobutyronitrile) as the initiator with similar results.

EXAMPLE 8

The procedure of Example 4 is followed using hydrogen peroxide-potassium persulfate redox catalyst with similar results.

EXAMPLE 9

The procedure of Example 4 was followed using t-butylperoxy benzoate. The PVP polymer obtained (K-90) had a relatively poorer water dissolution than the PVP polymer of Example 4.

EXAMPLE 10

A. Pharmaceutical tablets were prepared using acetaminophen as the active ingredient and 1% and 2% by weight of the PVP powder prepared as in Example 4. The tablet was immersed in water and the amount of tablet dissolved with time was determined.

B. A similar pharmaceutical tablet was prepared using PVP prepared using the t-butylperoxy benzoate initiator of Example 9.

The tablets thus prepared were compared with respect to water dissolution at various periods of shelf-life. The results are shown in Tables 2 and 3 below.

TABLE 2\*

<u>Ex. No.</u>	<u>Shelf-Life (months)</u>	<u>Total % of Tablet Dissolved</u>				
		<u>Immersion Time (min)</u>				
		<u>60</u>	<u>120</u>	<u>180</u>	<u>240</u>	<u>300</u>
10-A	0	36.4	52.8	63.0	70.4	77.0
10-B	0	33.6	50.4	61.1	68.9	75.4
10-A	1 at 45°C.	33.0	49.7	60.8	68.8	75.1
10-B	1 at 45°C.	30.4	46.3	56.3	63.8	69.6

\* 1% PVP level

TABLE 3\*

Ex. No.	Shelf-Life (months)	Total % of Tablet Dissolved				
		Immersion Time (min)				
		60	120	180	240	300
10-A	0	43.9	63.8	74.7	80.7	84.9
10-B	0	33.8	55.4	65.3	71.1	75.5
10-A	1 at 45°C.	42.5	59.3	69.1	76.1	81.1
10-B	1 at 45°C.	38.9	56.0	65.3	71.1	75.5

\* 2% PVP level

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The results shown in Tables 2 and 3 demonstrate that pharmaceutical tablets made with PVP prepared using t-amylperoxy pivalate as initiator dissolved in water at a significantly greater rate, e.g., after 1 month at 45°C., than similar tablets prepared using PVP binders made from t-butylperoxy benzoate initiated polymerizations.

#### EXAMPLE 11

The comparative experiments of Example 10 were repeated using hydrochlorothiazide as the active pharmaceutical ingredient in the tablet. Similar results were obtained with respect to dissolution rate of the tablet in water.

#### EXAMPLE 12

Comparative experiments also were carried out using acetylsalicylic acid, chloramphenicol, chlorpromazine, methyl paraben, sulfothiazole, trimethoprine, and various non-steroidal anti-inflammatory drugs as the active pharmaceutical ingredients at 1 and 2% levels in place of acetaminophen in Examples 10A and 10B. Similar differences in dissolution rates were obtained.

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## WHAT IS CLAIMED IS:

1. A pharmaceutical tablet having an enhanced dissolution rate even after an extended shelf-life consisting essentially of an active pharmaceutical ingredient and 0.5-10% by weight of PVP as a binder therefor, said PVP being prepared by polymerizing vinyl pyrrolidone in the presence of a polymerization initiator selected from a peroxyester free radical initiator whose thermal homolysis reaction provides free radicals which are weak hydrogen abstractors, an azo initiator, or a redox initiator, and said PVP is characterized by being a substantially linear; non-crosslinked polymer having a high degree of water solubility.

2. A pharmaceutical tablet according to claim 1 wherein said PVP has a residual initiator level of less than 500 ppm.

3. A pharmaceutical tablet according to claim 2 wherein said PVP product is subjected to a post-heat treatment to reduce the initiator level to less than 500 ppm.

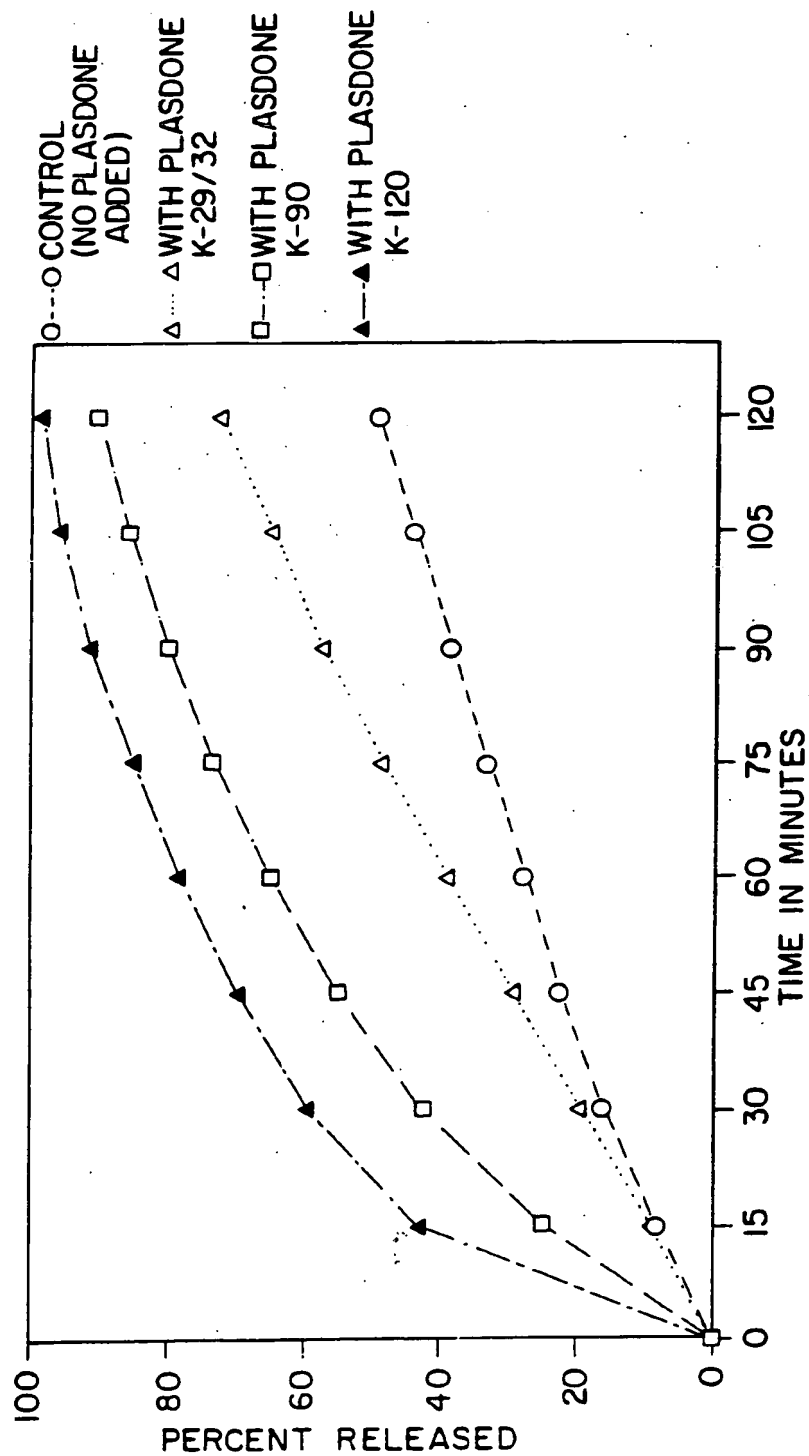
- 27 -

4. A pharmaceutical tablet which is characterized by an enhanced drug dissolution rate, low tablet friability and superior tablet compressibility consisting essentially of a pharmaceutically active ingredient and PVP having a K-value in excess of 116, preferably 119-140, as a binder, optionally with a filler or a lubricant, or both, prepared by wet granulation or direct compression, having a PVP viscosity average molecular weight of at least one million, a weight average molecular weight of at least two million and a relative viscosity of at least 1.20.

5. A pharmaceutical tablet according to claim 4 characterized by about 10-98% of a poorly water-soluble drug, about 2-10% of PVP K-116-140, about 0.5-2% of a lubricant, 0-3% disintegrant, and about 0-85% of a filler.

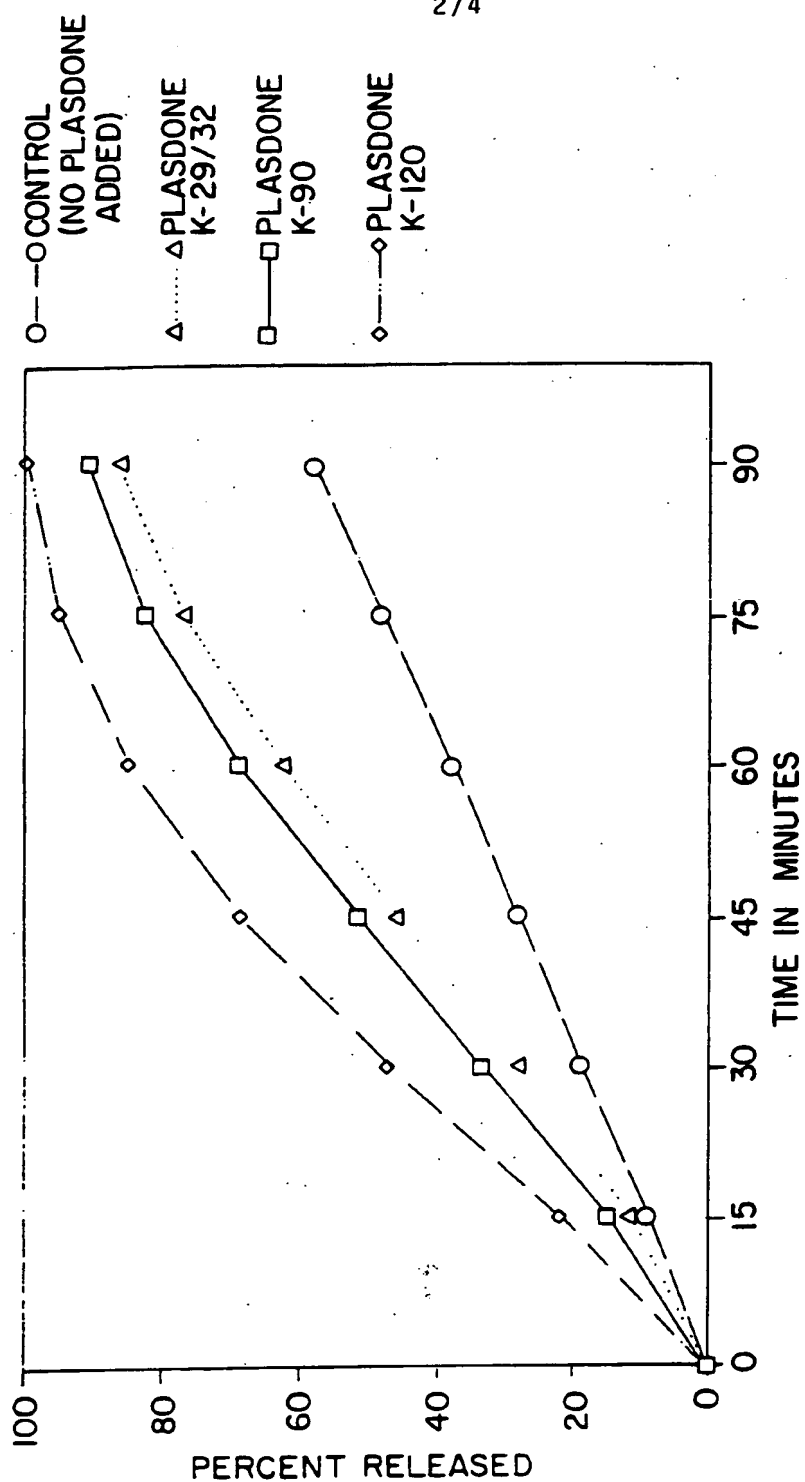
1/4

FIG. 1



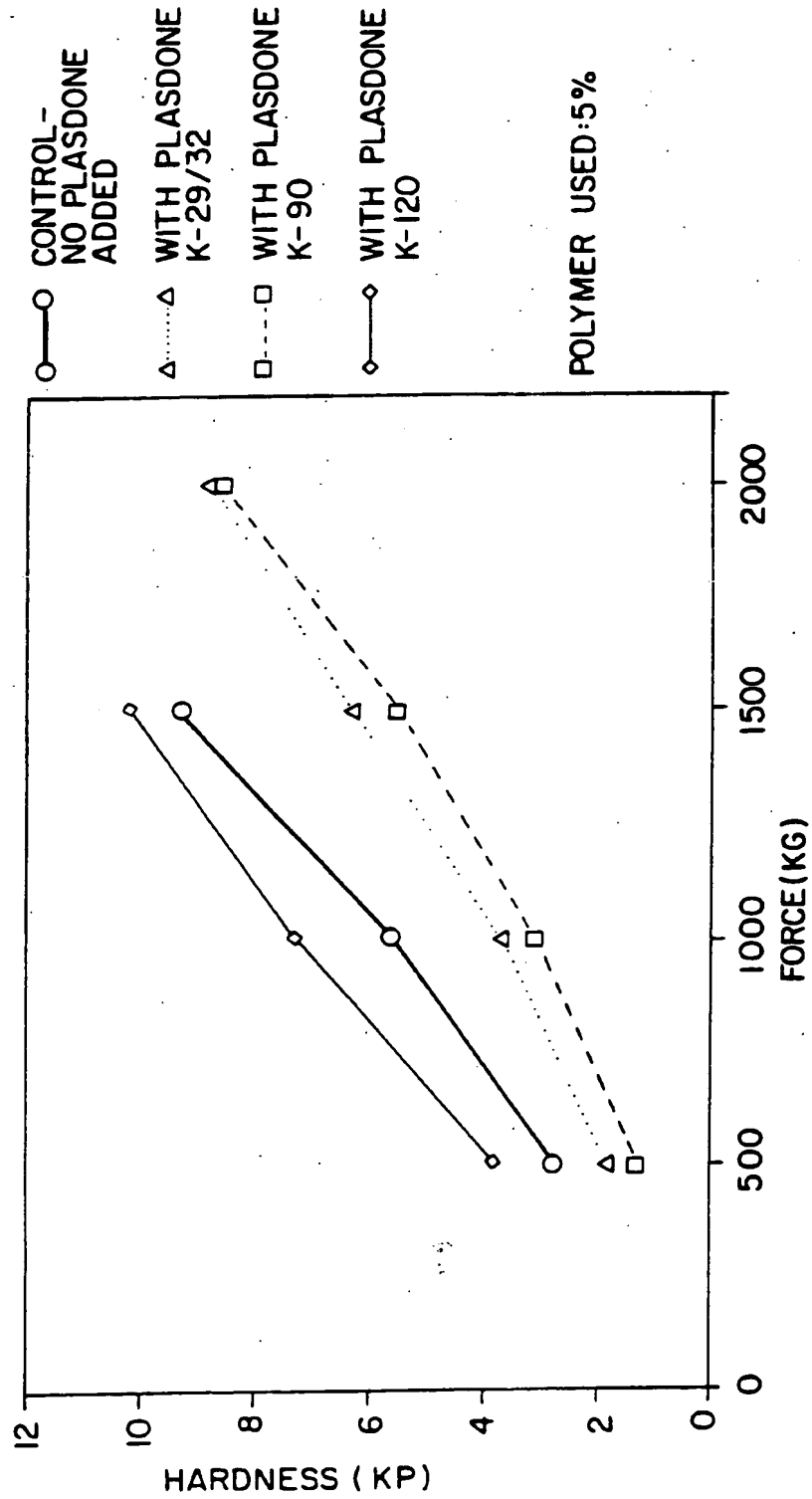
2/4

FIG. 2



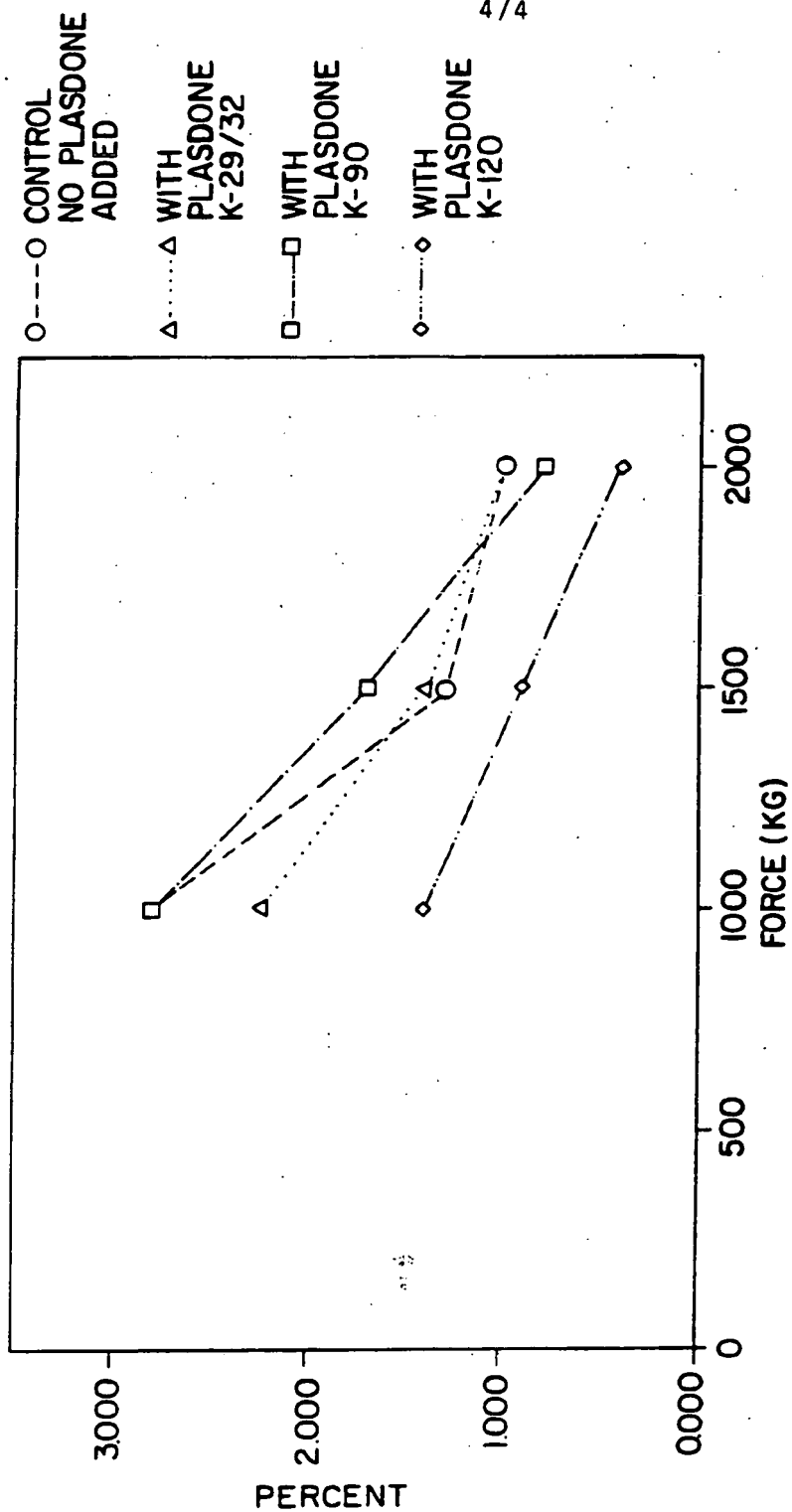
3/4

FIG.3



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FIG.4



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US92/09821**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) : A61K 9/14

US CL : 424/484

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/484, 467, 469, 473, 499

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,344,934 (MARTIN ET AL) 17 AUGUST 1982; See entire document.	1-5
Y	US, A, 5,009,897 (BRINKER ET AL) 23 APRIL 1991; See entire document.	1-5
Y	US, A, 5,035,897 (AYER ET AL) 30 JULY 1991 See entire document.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be part of particular relevance	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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* L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* G	document member of the same patent family
* O* document referring to an oral disclosure, use, exhibition or other means		
* T* document published prior to the international filing date but later than the priority date claimed		

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29 DECEMBER 1992

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Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Authorized officer

WILLIAM E. BENSTON, JR.

Facsimile No. NOT APPLICABLE

Telephone No. (703) 308-2351

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